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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/767,630	01/28/2004	Ursula K. Ehmann	STNUN.001A	5423

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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 01/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/767,630	EHMANN ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-9 and 11-20* is/are rejected.

7)☒ Claim(s) *2, 4 and 10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 September 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/21/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-20 are pending in the instant application.

Artifact 10767630CA, consisting of black and white drawings of Figures 1, 2, 3, 4a-f, 5a-d, 6a-e, and 7, is acknowledged.

Information Disclosure Statement

Receipt of an information disclosure statement, filed on 9/21/2004, is acknowledged. The signed and initialed PTO 1449 has been mailed with this action.

Drawings

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: parts a-f of Figure 4, parts a-d of Figure 5, and parts a-e of Figure 6. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

Claim 2 is objected to because of the following informalities: the limitation "wherein the human epithelial cells are human bladder epithelial cells" results in the recitation of an alternative that is not, in fact, an alternative. Appropriate correction is required.

Claim 15 is objected to because of the following informalities: the limitation "wherein the human epithelial cells are human bladder epithelial cells" results in a duplication of a limitation already encompassed by the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12, 19 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 is vague and indefinite in that the metes and bounds of the phrase "propagate the matrix" are unclear. The phrase is unclear in that the preamble of the claim recites "a method for providing a tissue matrix." Dorland's Illustrated Medical Dictionary defines the term tissue as an aggregation of similarly specialized cells united in the performance of a particular function. The phrase "propagate the matrix" could be describing the production of a matrix by the cells. However, to form a tissue, it appears as though cells added from the cell culture of claim 10

would need to divide to cover the matrix in order to form an organized tissue. Therefore, it is not clear whether the phrase "propagate the matrix" refers to the propagation of cells in contact with the matrix or the propagation of the matrix by the cells.

Claim 19 is vague and indefinite in that the metes and bounds of the claimed method are unclear. The preamble recites "an assay for studying human bladder epithelial cell-cell communication." However, it is not clear that utilizing the composition of matter comprising non-proliferating epithelial cells, human bladder epithelial cells or human epithelial cells of another luminal organ and medium will *necessarily* result in qualitative or quantitative data specific for any aspect of epithelial cell-cell communication. The step of utilizing does not provide specific positive action method step(s) that would clearly provide data relevant to the study of human bladder epithelial cell-cell communication. Therefore, it is unclear if one necessarily accomplishes what is intended for the method by practicing the recited method step.

Claim 20 is vague and indefinite in that the metes and bounds of the claimed method are unclear. The preamble recites "an assay for studying human bladder epithelial cell contact inhibition." However, it is not clear that utilizing the composition of matter comprising non-proliferating epithelial cells, human bladder epithelial cells or human epithelial cells of another luminal organ and medium will *necessarily* result in qualitative or quantitative data specific for any aspect of epithelial cell contact inhibition. The step of utilizing does not provide specific positive action method step(s) that would clearly provide data relevant to the study of human bladder epithelial cell contact inhibition. Therefore, it is unclear if one necessarily accomplishes what is intended for the method by practicing the recited method step.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 7, 8, and 13-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Taylor-Papadimitriou et al (Int J Cancer. Vol. 20, No. 6, pages 903-908, 1977; see the entire reference).

Taylor-Papadimitriou et al teach a method of culturing human mammary epithelial cells, comprising plating a confluent monolayer of non-proliferating calf lens epithelial cells and human mammary epithelial cells under conditions appropriate to allow the human mammary epithelial cells to proliferate (e.g. Abstract; page 903, *Fractionation and freezing down of milk cells, Recovery and culture of milk epithelial cells*; Table II, page 908, 1st full paragraph). Stedman's Online Medical Dictionary, 27th Edition, defines the mammary gland as the potential and active compound, alveolar, apocrine, milk-secreting gland that lies within the breast, in which the parenchyma of the resting postpubertal female gland consists of ducts. The ducts necessarily have a channel (i.e. lumen) and thus the mammary gland comprises epithelial cells of a luminal organ. The calf lens epithelial cells are non-proliferating as a result of mitomycin treatment (e.g. page 908, 1st full paragraph; page 904, *Preparation of mitomycin-treated feeders*). Further, Taylor-Papadimitriou et al teach the use of medium 199 containing 15% fetal calf serum (e.g. Figure 4; page 904, *Serum requirement of mammary epithelial cells*).

Prior to the addition of the human mammary epithelial cells, the confluent monolayer of calf lens epithelial cells is a composition of matter consisting essentially of non-proliferating epithelial cells and medium (e.g. page 903, *Recovery and culture of milk epithelial cells* and *Lens epithelial cells*).

Taylor-Papadimitriou et al teach a composition consisting essentially of human mammary epithelial cells (i.e. epithelial cells of a luminal organ other than bladder) and medium (e.g. page 903, *Fractionation and freezing down of milk cells, Recovery and culture of milk epithelial cells*).

Regarding claim 8, the term "about 10%" is interpreted to encompass a serum concentration of 15%.

Claims 1, 3, 5-8 and 13-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Barsky et al (US Patent No. 5,643,787; see the entire reference).

Barsky et al teach a method of culturing epithelial cells on a feeder layer of myoepithelial cells (e.g. the cell lines HMS-1 and HMS-X), comprising placing the epithelial cells onto the feeder layer and incubating the cultures to allow active mitogenesis (e.g. column 3, lines 51-67; column 4, lines 51-67). Barsky et al teach irradiation of the feeder layer to prevent further cell division, without killing the cells (e.g. column 4, lines 46-50). Epithelial cells taught by Barsky et al include HMS-1 myoepithelial cells, HMS-3 salivary gland epidermoid carcinoma cells, MCF-7, MDA-MB-231 breast adenocarcinoma cells, 10 primary prostate carcinoma cultures, 10 primary breast carcinoma cell cultures, and 5 breast carcinoma in situ cultures (e.g. column 19, lines 1-21). Feeder layer cells taught by Barsky et al include HMS-1 and MCF-7 breast

carcinoma cells (e.g. column 19, lines 1-21). Dorland's Illustrated Medical Dictionary defines carcinoma as a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Dorland's Illustrated Medical Dictionary defines the prostate as being made up partly of glandular matter, whose ducts empty into the prostatic portion of the urethra. Stedman's Online Medical Dictionary, 27th Edition, defines the mammary gland as the potential and active compound, alveolar, apocrine, milk-secreting gland that lies within the breast, in which the parenchyma of the resting postpubertal female gland consists of ducts. Ducts comprise lumens and thus the prostate and breast are luminal organs. Further, ATCC defines MCF-7 cells as human mammary epithelial cells. Therefore, the cells taught by Barsky et al are non-proliferating epithelial cells and human epithelial cells of a luminal organ other than the bladder.

Prior to the seeding of the human epithelial cells, the feeder layer taught by Barsky et al is a composition of matter consisting essentially of non-proliferating epithelial cells and medium (e.g. column 19, lines 1-21).

Prior to irradiation of the 80-90% confluent feeder layers as taught by Barsky et al, the composition of matter consists essentially of MCF-7 breast carcinoma cells (i.e. human epithelial cells of a luminal organ other than bladder) and medium (e.g. column 19, lines 1-21).

Claims 11 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Atala et al (WO 93/07913; see the entire reference).

Claim 11 is drawn to an artificially engineered human bladder epithelial tissue matrix comprising cells from the cell culture of claim 10. Claim 12 is drawn to a method for providing

a tissue matrix for bladder repair comprising contacting cells from the cell culture of claim 10 with an acellular tissue matrix under conditions appropriate for the cells to "propagate the matrix." The cells of claim 10 comprise human bladder epithelial cells and non-proliferating epithelial cells. The phrase "cells from the cell culture of claim 10" is read broadly as encompassing contacting the human bladder epithelial cells in the presence or absence of the non-proliferating epithelial cells. The phrase "propagate the matrix" is interpreted as the proliferation of cells in contact with the matrix (see the rejection under 35 USC § 112, 2nd paragraph).

Atala et al teach methods and artificial matrices for the growth and implantation of urological structures and surfaces, comprising the growth of urothelial cells on a matrix formed of a bioabsorbable or biodegradable, synthetic polymer, and, in some embodiments, the polymer is enhanced by coating with compounds such as basement membrane components (e.g. page 6, lines 3-5; page 11, lines 22-33). The urothelial cells may be from an established cell line or may be derived from the host or a related donor by introducing a catheter into the bladder to fill the bladder with an enzyme solution that allows the collection of urothelial cells from the bladder following irrigation (e.g. page 11, lines 2-9; page 14, lines 19-20). Atala et al teach that once the cells have begun to grow and cover the matrix, they are implanted in the patient at a site appropriate for attachment, growth and function (e.g. page 11, lines 11-13).

Claims 13-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Ehmann et al (Experimental Cell Research, Vol. 243, pages 76-86, 1998; see the entire reference).

Ehmann et al teach a composition of matter consisting essentially of rat mammary cells of the LA7 line, which were inactivated by a single dose of irradiation in a flask, and medium (e.g. page 77, right column and paragraph bridging pages 77-78). Further, Ehmann et al teach that the LA7 feeder cells are capable of forming tight junctions with mouse mammary epithelial cells (e.g. paragraph bridging pages 81-82) and thus should be capable of forming tight junctions with human epithelial cells

Claims 13-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Vatne et al (Anticancer Research, Vol. 18, pages 3985-3990, 1998; see the entire reference).

Vatne et al teach a composition of matter consisting essentially of malignant urothelial cells (HYu-1703 He), which originate from a human, invasive urinary bladder tumor, and complete DMEM medium (e.g. Abstract; page 3985, *Tumor cells*). Vatne et al teach a method of using said composition of matter comprising collecting tumor spheroids from the composition of matter; transferring the spheroids to a dish with five day old bladder fragments with or without an intact epithelium; coculturing the spheroids and bladder fragments; and fixing the cocultures for light microscopy (e.g. page 3985, *Confrontation culture*). Further, Vatne et al teach that this method can be used for studies of cell-cell adhesion and factors that regulate different steps in tumor invasion (e.g. page 3988, right column, last paragraph). Dorland's Illustrated Medical Dictionary defines the term contact inhibition as the inhibition of cell division and cell motility in normal animal cells when in close contact with each other. Tumor invasion is a measure of cell motility and thus can be used to study contact inhibition. Therefore, Vatne et al teach the use of a composition of matter consisting of bladder epithelial cells and medium to study cell-cell communication and contact inhibition.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor-Papadimitriou et al (Int J Cancer. Vol. 20, No. 6, pages 903-908, 1977; see the entire reference) in view of Smith et al (Cancer Res. Vol. 41, No. 11 Pt 1, pages 4637-4643, 1981; see the entire reference).

The teachings of Taylor-Papadimitriou et al are described above and applied as before.

Taylor-Papadimitriou et al do not teach the use of serum at a concentration at about 0.5% and do not teach the culturing of human tumor epithelial cells of a luminal organ.

Smith et al teach the culture of nonmalignant and malignant mammary epithelial cells on an irradiated fibroblast feeder layer in enriched medium for mammary cells (MM) comprising

0.5 % unfrozen newborn or fetal calf serum (e.g. page 4637, left column; page 4638, right column; Table 2; page 4641, left column, 1st full paragraph). Smith et al state the following with regard to the benefits of using the disclosed culture conditions (see page 4641, left column, 1st full paragraph):

> The use of feeder layers to culture human mammary epithelial cells was first reported by Taylor-Papadimitriou et al (Int J Cancer. Vol. 20, No. 6, pages 903-908, 1977). However, even under optimal conditions, they needed to plate approximately 10^6 cells in order to obtain 75 to 100 epithelial patches in primary culture...In contrast, we have observed a high efficiency (1 to 50%) of colony formation by cells in secondary culture from nonmalignant and malignant specimens when feeder layers were used in conjunction with specific conditioned media, hormones and growth factors.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the culture conditions of Taylor-Papadimitriou et al to include the culturing of malignant mammary epithelial cells and the media comprising 0.5% serum as taught by Smith et al because Taylor-Papadimitriou et al teach it is within the ordinary skill in the art to use serum in medium for the culture of mammary epithelial cells on a feeder layer and Smith et al teach the use of a reduced serum concentration for the culture of malignant and nonmalignant mammary epithelial cells on a feeder layer.

One would have been motivated to make such a modification in order to receive the expected benefit of high efficiency colony formation relative to the method of Taylor-Papadimitriou et al as taught by Smith et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Relevant Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Fentiman et al. Cultured human breast cancer cells lose selectivity in direct intercellular communication. Nature. Vol. 269, No. 5624, pages 156-158, 1977. Fentiman et al teach the transfer of 5-^{3}H-uridine from pre-labeled breast cancer epithelial cells to lens epithelial cells in culture (e.g. Figure 1; page 157, right column). The junctions between the cells are apparently gap junctions.

Southgate et al. "Culture of Human Urothelium" in Culture of Epithelial Cells, Second Edition. Edited by R. Ian Freshney and Mary G. Freshney, Wiley-Liss, Inc., 2002, pages 381-399.

Conclusion

No claims are allowed.

Claims 2, 4 and 10 are objected to as depending upon a rejected claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jennifer Dunston
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PRIMARY EXAMINER